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13. ABSTRACT (Maximum 200 Words) <p>The purpose of this research is to investigate whether eating brown seaweed (<i>Undaria pinnatifida</i>) can influence breast cancer risk. Brown seaweeds are popular in Japan, where the incidence of breast cancer is about 1/6 the rate of that reported for American women. In several animal studies of diet and cancer, adding seaweed to the normal diet resulted in longer healthy lives. In particular, we will examine cell surface binding characteristics and protein expression associated with the consumption of dietary seaweeds by women who have been treated for Stage 3 breast cancer.</p> <p>To date, progress has been limited by the lack of approval from HSRRB (Proposal Log Number BC972552, HSRRB Log Number A-8050), with modifications. Modifications have been submitted in March, the Memorandum for Record has been filed, and we are completing the scientific review and modifications of the study. Final approval has not yet been granted. However, when this grant was first awarded in 1999 to the University of Massachusetts, we did a preliminary study to assess potential toxicity of dietary seaweed. The first paper on iodine content in commercially available seaweeds has been published, as has a review of the health effects and bioavailability of seaweed iodine in brown seaweeds.</p>					
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INTRODUCTION

Breast cancer is the second leading cause of cancer among American women. Survival rates at 5 years average 87%, decreasing to 77% at 10 years, 63% at 15 years, and 52% at 20 years(1). Although current use of tamoxifen and letrozole may have a significant impact on long term survival in the future, an estimated 39,800 American women will die of breast cancer in 2003 (1). There is an urgent need for new treatments for metastatic breast cancer and chemoprevention that can be used to prevent breast cancer recurrence.

Epidemiologic studies comparing breast cancer rates among Japanese women in Japan and American women in the US are supportive that dietary factors could be critical to understanding breast cancer rates. In vitro work using seaweed extracts have shown high antitumor activity. In vivo work using rats and mice have demonstrated that seaweed, both as part of a regular diet, as an extract in drinking water, and as extracts which were injected into tumor bearing rats, have all confirmed that something in seaweed inhibits cancer formation and can cause tumor remission/tumor rejection in tumor bearing animals.

Although little is known about relative breast cancer risk and seaweed intake among humans, a small body of research, both *in vivo* and *in vitro*, suggests seaweed may be useful in breast cancer prevention. Seaweeds are specifically used to treat tumors in Traditional Chinese Medicine and Japanese folk medicine. On a population level, those people for whom seaweed is a regular part of their diet, most notably in Japan, have dramatically lower rates of hormone sensitive cancers, both of the breast and prostate . Epidemiologic studies done in Japan in the 1980s, before Westernized diets were common, reported that Japanese women had 1/3 the rate of premenopausal breast cancer and 1/9 the rate of postmenopausal breast cancer . In addition, when a Japanese woman developed breast cancer, she was more likely to survive at least five years than a woman diagnosed with breast cancer in the United States (3).

No clinical studies of breast cancer and seaweed have yet been done, however, in a large prospective dietary study 21,852 Japanese nurses in Japan, investigators reported after 9 years of follow-up, that high intake of miso (fermented soybean paste) soup was the food most closely associated with the lowest breast cancer risk. This is particularly interesting since an *in vivo* study compared dietary seaweed water extract to powdered seaweed and to injected seaweed extract, and reported that dietary seaweed water extract was the most effective against induced tumors . Since miso soup is made from a concentrated hot water extract of seaweed plus a tablespoon or less of miso (soybean paste) and usually a few vegetables, it is very suggestive that seaweed and seaweed soup consumption may help explain the lower breast cancer rates of women in Japan. Women who had three or more bowls of miso soup each day had about half the rate of breast cancer (RR 0.51; 95% Confidence Interval 0.32 to 0.83). In two other epidemiologic studies of diet and breast cancer in Japan, 15% lower rates of breast cancer were associated with daily miso soup consumption, (4) and 13% lower rates for women who drank miso soup at least five times /week.

Seaweed are also rich sources of iodine(5). Iodine deficiency may be a risk factor for breast cancer . Additionally, some physicians have reported therapeutic success using oral elemental iodine solution for breast fibrocystic disease . Iodine is critical for the health of newborn infants, and during lactation iodine is concentrated in breast milk and is found in rapidly dividing breast cells. When rapidly dividing breast cancer cells are present in the breast, iodine may also play a role, although the exact mechanism is unclear. Breast cancer cells have lower iodine content than nearby healthy breast cells, and the work of Funahashi and colleagues report protection from dimethylbenzanthracene (DMBA)-induced mammary tumors when iodine was given to the rats in their diet. As a possible mechanism, they reported a high correlation between serum iodine and apoptosis of mammary cancer cells . These results, along with those we and others have reported for dietary seaweed as inhibitory of DMBA-induced mammary tumors are consistent with the idea that seaweed, possibly via iodine, could be involved in breast cancer prevention.

We were interested in providing a similar amount of seaweed to that eaten in Japan. On average, seaweed intake in Japan is estimated between 7 and 10 g/d dry weight(5). The bioavailability of the seaweed iodine to humans has been reported , and we have therefore chosen a low-iodine seaweed for this study. On average, *Undaria pinnatifida* contains 50 μ iodine/g. 5 grams of *Undaria* will provide an additional 250 μ iodine/d, well under the 1,000 μ iodine/d that is considered the maximum tolerated dose of iodine/d.

BODY

This research project was begun in 1999, at the University of Massachusetts. However, only the initial work on seaweed toxicity was completed before the PI moved to the University of South Carolina. This coincided with the necessity of obtaining Army IRB approval, and although numerous renditions of the grant have now been made, and tentative Army IRB approval was given in August 2003, the study was not officially approved, and further changes have been made to the study design. The Memorandum for Record has been completed, and we are in the process of obtaining scientific review for the revised study and making final corrections to the Informed Consent and Protocol. We anticipate submission of these revisions by June 10, 2005.

We have redesigned the study to include greater analysis of fewer subjects. This reflects both the lack of significant hormonal changes in a previous study of dietary seaweed and the findings of significant changes in cell surface binding characteristics associated with dietary seaweed. These cell surface binding sites are particularly important in breast cancer metastases, CXCR4 and CCR5 (10). CXCR4 appears to act as a homing signal for metastatic breast cancer cells, binding exclusively to stromal derived factor-1, a cytokine found most abundantly in the liver, lung, and bone, all preferred sites for breast cancer metastases. The role of CCR5 is less well understood in breast cancer metastasis, but is also considered crucial in breast cancer(11). We will use standard flow cytometry to identify the relative binding site densities and in-depth proteonomics to indicate which proteins are involved in both binding site activation and responses to dietary seaweed. Based on concurrent work on breast cancer and CXCR4 and CCR5 changes on CD4 and CD8 cells associated with dietary seaweed as measured by flow cytometry, we will focus on serum T lymphocytes.

Profiling of serum proteins using surface enhanced laser desorption/ionization time of flight (SLEDI-TOF) mass spectrometry has become increasingly specific and can now identify with high sensitivity and specificity cancer types, including breast cancer based on the specific signature of proteomic serum biomarkers. Recent studies (reviewed by Laronga (12 2004 2004)) have shown that using SLEDI-TOF can differentiate between BrCa1 carriers and healthy controls (13/15 women with BrCa1 compared to one of the 15 non-carriers), 14/16 patients with breast cancer even 6-9 months following treatment for breast cancer, compared to healthy controls, and sentinel lymph node positive (22/27) patients from sentinel lymph node negative (55/71) patients. SELDI ProteinChip® technology is the primary proteomic platform technology for the NCI Early Detection Research Network (EDRN) study of early detection serum biomarkers of prostate cancer (e.g., review by Grizzle et al.(13), 2004; other prostate diseases (e.g., review by Fung 2004), Semmes et al., 2005(14)), ovarian cancer (15) and. In addition, SELDI ProteinChip® technology has been used to identify changes in serum protein expression with the addition of novel foods, like green tea, to the diet (16).

The purpose of this research is to investigate whether consuming brown seaweed (*Undaria pinnatifida*) can change lymphocyte populations, surface binding sites on CD4 and CD8 cells, and alter serum protein expressions. Specifically we will study CXCR4 and CCR5 cytokine receptor sites, both known to be important in determining location of

breast cancer metastases. To minimize the variation with menstrual cycle phase, and to concentrate on the age group with the highest risk of breast cancer, we will focus on postmenopausal women. Based on our *in vitro* studies showing that seaweed extract has a dose dependent inhibitory effect on estrogen receptor negative (ER-), but no effect on estrogen receptor positive (ER+) breast cancer cells, we anticipate that estrogen receptor status will be an important variable in our study. A blinded, crossover study design will serve to address the issues of any carry-over effect of seaweed after cessation of seaweed intake.

In a second study done at the University of Massachusetts on the bioavailability of seaweed iodine has now been submitted to the *American Journal of Clinical Nutrition*. Our conclusions were that although 5 grams/day of seaweed, the average daily consumption in Japan, was associated with a statistically significant increase in thyroid stimulating hormone, the increase was small and not biologically important. All clinical values remained within normal limits. This means that our next intervention will be done with a clinically proven safe level of iodine-containing seaweed. The two manuscripts are included in the appendix.

Two book chapters reviewing the health effects of consuming brown seaweeds have been conducted, one of which is in press, and the other is in the final stages of review. The completed manuscript is included in the appendix.

KEY RESEARCH ACCOMPLISHMENTS

In March 2005, we redesigned the study to better reflect the current state of knowledge regarding the health effects of dietary seaweed and breast cancer.

Evaluation of iodine content and bioavailability of commercially available dietary seaweeds
The original work begun at the University of Massachusetts has now been completed. We first assessed the potential toxicity of dietary seaweeds for use in our research by collecting and analyzing commercially available dietary seaweeds for their iodine content. The paper reporting our findings has now been published by *Thyroid*. Based on our work, we identified *Undaria pinnatifida*, *Alaria esculenta*, and *Sargassum muticum* as having safe levels of iodine.

Reviews of health effects associated with consuming dietary brown seaweeds

REPORTABLE OUTCOMES:

Manuscripts:

Jane Teas, Lewis E. Braverman, Mindy S Kurzer, Sam Pino, Thomas G. Hurley, James R. Hebert. Seaweed and Soy: Companion Foods in Asian Cuisine and Their Effects on Thyroid Function in American Women. *Thyroid* 14(10):836-841.

Jane Teas. Dietary Brown Seaweeds and Human Health Effects. In: *Seaweed Resources*. Ed: Critchley, Alan T , Masao Ohno and Danilo Largo. Publisher Expert Centre for Taxonomic Identification, Univ. Amsterdam. 2005.

J.Helen Fitton, Jane Teas. Marine algae and polysaccharides with therapeutic applications. In: *Marine Nutraceuticals*. Ed: Colin Barrow CRC Press. In Preparation.

Poster presentations

Effect of Seaweed Ingestion on Thyroid Function in Postmenopausal Women (P3-675). (Jane Teas, Sam Pino, Thomas G. Hurley, Alan Critchley, Lewis E. Braverman). **Endocrinology Society Annual Meeting**, Philadelphia, PN June 2003.

Funding applied for and awarded

Dietary Algae as a Modulator of Breast Cancer Metastases: An exploratory Grant to Document Proof of Principle (**Principal Investigator: Jane Teas**). Cancer Prevention and Cancer Control (Department of Defense Award to encourage collaboration between the Medical University of South Carolina and the University of South Carolina). Awarded December 2003.

Dietary Algae and Breast Cancer. University of South Carolina preliminary grant to be used in application for NIH funding of a Cancer Complementary and Alternative Medicine Center. (**Principal Investigator: Jane Teas**). Awarded May 2004.

CONCLUSIONS

Beyond the great variability of iodine in brown seaweed and its bioavailability to humans, we can not make any conclusions until we have data.

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APPENDICES

1. Jane Teas, Sam Pino, Alan Critchley, Lewis E. Braverman. Variability of Iodine Content in Common Commercially Available Edible Seaweeds. *Thyroid*. 14(10):836-841.
2. Jane Teas. Dietary Brown Seaweeds and Human Health Effects. In: **Seaweed Resources**. Ed: Critchley, Alan T , Masao Ohno and Danilo Largo. Publisher Expert Centre for Taxonomic Identification, Univ. Amsterdam. 2005.

Variability of Iodine Content in Common Commercially Available Edible Seaweeds

Jane Teas,¹ Sam Pino,^{2,3} Alan Critchley,⁴ and Lewis E. Braverman³

Dietary seaweeds, common in Asia and in Asian restaurants, have become established as part of popular international cuisine. To understand the possibility for iodine-induced thyroid dysfunction better, we collected samples of the most common dietary seaweeds available from commercial sources in the United States, as well as harvester-provided samples from Canada, Tasmania, and Namibia. Altogether, 12 different species of seaweeds were analyzed for iodine content, and found to range from 16 $\mu\text{g/g}$ (± 2) in nori (*Porphyra tenera*) to over $8165 \pm 373 \mu\text{g/g}$ in one sample of processed kelp granules (a salt substitute) made from *Laminaria digitata*. We explored variation in preharvest conditions in a small study of two Namibian kelps (*Laminaria pallida* and *Ecklonia maxima*), and found that iodine content was lowest in sun-bleached blades ($514 \pm 42 \mu\text{g/g}$), and highest amount in freshly cut juvenile blades ($6571 \pm 715 \mu\text{g/g}$). Iodine is water-soluble in cooking and may vaporize in humid storage conditions, making average iodine content of prepared foods difficult to estimate. It is possible some Asian seaweed dishes may exceed the tolerable upper iodine intake level of 1100 $\mu\text{g/d}$.

Introduction

IODINE WAS FIRST IDENTIFIED as an element based on the observations of Courtois in 1811 that sulfuric acid-treated seaweed ash produced a purple vapor that condensed into purple crystals (1). For many decades, seaweeds were the primary source of iodine for medicinal purposes, only being supplanted by the discovery that iodine could be extracted from silver and saltpeter mining deposits. These mineral sources were less expensive than collecting seaweed and burning it, and by the late 1930s, seaweed was no longer used as an iodine source (2). In the United States, seaweeds have also been used to enrich soil, as sources of inexpensive minerals for animal food supplements, and recently, as food and a natural source of iodine and other minerals in health supplements.

In an earlier study, we and others reported that dietary seaweed delayed the time to tumor onset in a rat dimethylbenzanthracene mammary-induced cancer model (3–7). In preparation for a clinical study in humans, it was necessary to evaluate common edible seaweeds for iodine content since excess iodine intake might adversely affect thyroid function. We present our findings for 12 different edible seaweeds, and evaluate factors that modulate seaweed iodine content.

Seaweeds have been a part of the world's ecosystem for 2 billion years (8), during which time they have changed lit-

tle. Although archaeological evidence for the use of seaweeds is hampered by its easily degradable nature, it is likely that seaweeds have been part of traditional diets of coastal dwelling peoples worldwide. Seaweeds have been used by humans as medicine and food for at least 13,000 years. Based on discoveries of seaweeds found at Monte Verde, a late Pleistocene settlement in Chile (9,10) and archeological inference from ancient sites of the Jomon period in Japan (11), seaweeds have been included in three of the major medical traditions: Ayurvedic medicine from the fourth century BC (12); Traditional Chinese Medicine, with its first reference to its medicinal qualities reportedly made by Shen-nung in the Chinese *Materia Medica* of 2700 BC (13); and in the Ebers Papyrus, the Egyptian treatise on medical care, written approximately in 1550 BC (14). The medicinal uses of seaweed are vast and range from topical burn therapy to goiter therapy to softening of tumors (15). As food, seaweeds have been treasured by the nobility of Japan and China, as well as commoners such as fishermen living along the coast. In 600 BC, Sze Teu wrote, "Some algae are a delicacy fit for the most honored guests, even for the King himself (11)." Tax records from the eighth century indicate that more than 30 kinds of seaweed were listed as tax payments to the Japanese government (11). National Seaweed Day (February 6) in Japan commemorates this official recognition of the value of seaweed (16), and the continuing high status of seaweed in

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TABLE IODINE CONTENT OF COMMERCIALY AVAILABLE EDIBLE SEAWEEDS

Genus and species	Common name ^a	Harvest location	Form	n	Total iodine ($\mu\text{g/g}$)	SD
<i>Alaria esculenta</i>	American wakame	Maine	Whole	7	110	30
		Maine	Whole	5	431	104
<i>Ascophyllum nodosum</i>	Knotted wrack	Maine	Whole	3	646	392
<i>Ecklonia maxima</i>	Paddle weed	Namibia	Whole	6	2123	352
<i>Eisenia bicyclis</i>	Arame	Japan	Whole	3	586	56
<i>Fucus vesiculosus</i>	Bladderwrack	Maine	Whole	3	276	82
<i>Hizikia fusiforme</i>	Hijiki	Japan	Whole	6	629	153
<i>Laminaria</i>	Kelp					
	Oarweed					
	(<i>L. longicruris</i>)	Maine	Whole	3	746	26
	Kelp ^b	British Columbia Canada	Capsule	5	1259	200
	Kombu ^b	Washington	Whole	7	1350	362
	Wild kelp ^b	Maine	Capsule	7	1356	665
	Kelp ^b	British Columbia Canada	Whole	5	1513	117
	Oarweed	Maine	Whole	6	1862	520
	Fingered tangle					
	(<i>L. digitata</i>)	Maine	Whole	6	1997	563
	Mitsuishi-kombu					
	(<i>L. angustata</i>)	Japan	Powdered	4	2353	65
	Fingered tangle	Maine	Whole	6	2984	910
	Fingered tangle	Iceland	Granules	6	8165	373
<i>Palmaria palmata</i>	Dulse	Maine	Whole	3	72	23
<i>Porphyra tenera</i>	Nori, purple laver	Japan	Sheet	3	16	2
<i>Postelsia palmaeformis</i>	Sea palm	California	Whole	7	871	231
<i>Sargassum</i>	Horsetail tangle,	Washington	Whole	5	30	1
<i>Undaria pinnatifida</i>	Mekabu (Undaria spore)	Tasmania	Tablets	4	22	1
	Wakame	Tasmania	Powder	5	32	4
	Wakame	Tasmania	Whole	4	41	14
	Wakame	Japan	Whole	6	42	17
	Mekabu	Tasmania	Powder	5	53	3
	Wakame	New Zealand	Whole	6	115	42

^aCommon names according to Madlener (42) and Arasaki and Arasaki (11).

^bNo species indicated.

Japanese culture. In a recent article on improving public health nutrition in Japan, a recommendation for increasing seaweed consumption was included (17).

The actual amount of seaweed consumed is difficult to quantify because it is often as flavoring to noodles, soups, garnishes, and added as part of mixed vegetable dishes, as well as being a food that is served as a distinct entity as a snack, salad or side dish. In addition, seaweed is a part of military and religious ceremonial celebration foods in Japan. Soups containing seaweed (*miso* or *wakame*) have traditionally been included as part of most meals in Japan (8), although this is changing toward more Western foods (18). Estimated iodine intake of people in Japan, mostly from seaweed, ranges from 200 to 20,000 $\mu\text{g/d}$, with the average estimate of 500–1000 $\mu\text{g/d}$ (19). The average seaweed intake in Japan is approximately 4–7 g/d (11,20,21). Commercial data on seaweed sales in Japan estimate that the national average seaweed consumption per person is 4 kg/yr, or closer to 10 g per person per day (22).

In Japan, 21 species of seaweed are routinely included in the diet and in Korea more than 40 kinds of seaweed are commonly used as food (11). Elsewhere in the Pacific basin, in Hawaii and other Polynesian islands, 29 kinds of seaweed

have been reported as food, medicine, and as part of religious celebrations in precolonial times (23,24), and seaweeds are still part of the diets of many indigenous people living in Asia, Polynesia and the Pacific Islands.

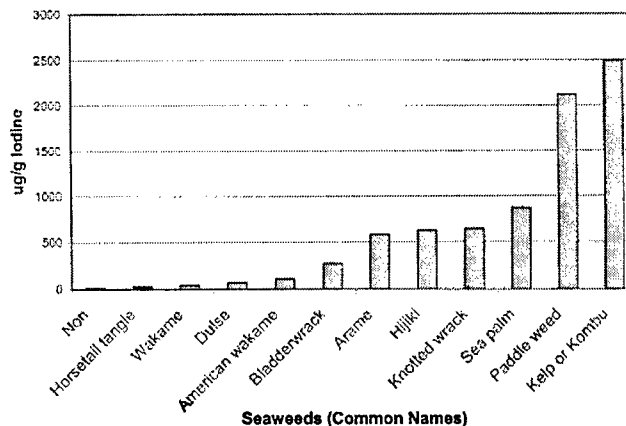


FIG. 1. Iodine content of dietary seaweeds compared by species.

TABLE 2. COMPARISON OF SEAWEED IODINE BY GENUS, GEOGRAPHIC LOCATION, AND STUDY

	<i>This study</i> $\mu\text{g/g}$	<i>Lee et al.</i> (31) $\mu\text{g/g}$	<i>Hou and Yan</i> (43) $\mu\text{g/g}$	<i>Aquaron et al.</i> (30) $\mu\text{g/g}$	<i>Van Netten et al.</i> (44) $\mu\text{g/g}$
Seaweed origin	U.S., Canada, Namibia, Tasmania, Japan	UK	China	France	British Columbia
<i>Arame</i>	586	714 ^a			600
<i>Dulse</i>	72	44			
<i>Hijiki</i>	629	391			436
Kelp granules. tablets (salt substitute)	8165	67			815
Kelp/kombu	1542 ^b	2650	3040	5307	2110
<i>Nori</i>	16	43	36		17
					185
<i>Wakame</i>	66 ^c	161 ^a	1571		60
					102
<i>Alaria</i>					151

^aAverage of two reported values.

^bAverage of 10 kinds of kelp analyzed.

^cAverage of three sample sites.

humid conditions, in which moisture might condense to concentrate water soluble iodine from the seaweed.

Additional factors known to affect iodine content of seaweed are season, salinity of the water, and depth of the seaweed, coldness of the water, distance from the equator, post-harvest storage conditions, and possibly other factors (32).

Other factors that affect the iodine content of seaweed include the part of the seaweed used. The stipe (stalk), although generally regarded as inedible, could be included in specimens harvested for health food supplements. In our study, the meristematic tissue at the base of the blade had the highest iodine content. Harvesting regulations in places such as Maine require leaving the base and at least 16 inches of seaweed, including the holdfast, stipe, and first few inches of the blade, which would include the meristematic tissue, on the rock. If harvesters did this, consumers would be protected from the high iodine containing meristematic tissue. However, harvesters do not routinely follow these guidelines either in the United States or internationally (33).

Food preparation and cooking methods are other factors in determining final iodine content of foods. Iodine in seaweed is highly water-soluble. One study of the effects of cooking on kelp reported that after 15 minutes of boiling, 99% of the seaweed iodine could be found in the cooking water (34). Although not specifically related to seaweed iodine, cooking loss of iodine from iodized salt has been studied. Goindi et al. (35) reported that the method of cooking was important in iodine loss, with losses ranging from 6% when roasted, to 20% when steamed or deep fried, to 27% when shallow fried, to 37%–82% with boiling (36). Although the previous values are for iodine in other foods, it is likely that cooked seaweed would be subject to similar rates of loss.

A meal is never made from only seaweed. Seaweed, when eaten in a meal with other foods with goitrogenic potential, such as cassava, *Brassica* (broccoli, cabbage, cauliflower, bok choy, etc.) and soy, may mitigate the effect of the high iodine in the seaweed.

The activity level of the person eating the seaweed has also been reported to be significant in terms of assessing exposure to seaweed iodine (37). In a study of Japanese male university students, iodine losses in sweat during athletic training were high, suggesting that exercise in hot humid climates could increase iodine daily requirements.

Although exposure to high concentrations of iodine will transiently decrease thyroid hormone synthesis for approximately 24 hours (acute Wolff-Chaikoff effect [38]), continued exposure to excess iodine results in a decrease in the iodide concentrating ability of the thyroid by decreasing the thyroid sodium iodide symporter (NIS), permitting normal thyroid hormone synthesis to resume (38,39). However, some individuals do not escape or adapt to the transient decrease in iodine-induced thyroid hormone synthesis (i.e., those with autoimmune thyroid disease [Hashimoto's thyroiditis]), and continued excess iodine ingestion may induce hypothyroidism (40). Thus, excess ingestion of seaweeds could, in susceptible subjects, induce hypothyroidism and, far less commonly in the United States, hyperthyroidism. Episodic dietary exposure to high-iodine-containing foods could pose health risks for iodine sensitive patrons. For example, the iodine content of nori, the flat sheets of seaweed used to make sushi, contain trivial amounts of iodine (16 $\mu\text{g/g}$), but a bowl of miso soup made with a kelp flavored stock, even without the presence of seaweed in the final soup, could contain more than 1000 μg of iodine. These sources of natural variation in iodine content contribute to the confusion in describing a particular species as "safe" for iodine sensitive individuals.

Seaweed iodine presents an interesting study in how people in Japan and Korea, with habitual exposure to seaweed-containing diets could be relatively immune to any effects of high iodine intake, but a single seaweed rich Japanese meal could present health risks to iodine sensitive unhabituated diners in low-iodine consuming countries. A greater awareness of the variability of iodine content of seaweeds will help in defining high-risk foods for sensitive individuals.

The observation of Paracelsus (1493–1541), the founder of toxicology, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy" (41), may need to be amended for iodine in seaweed. The safe dose of seaweed may depend on the kind of seaweed, but also the storage conditions, cooking methods, the climate where the person resides, the amount of physical exercise a person does, the presence of goitrogenic foods eaten with the meal, and the frequency of seaweed consumption.

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Dietary Brown Seaweeds and Human Health Effects

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Introduction

Seaweeds have been a part of the world's ecosphere for two billion years (Guiry 2003). Sun-baked, pounded by turbulent waves, and often submerged in an ever-changing sea of bacteria, viruses, and herbivorous predators, they have changed little, having evolved unique defense mechanisms that largely preclude degradation as long they are growing. Iodine may be part of the chemical defense strategies used by seaweeds to deter predation. Although several chemicals found abundantly in seaweeds are not found elsewhere, iodine was the first applied use of seaweeds in modern medicine. Most brown seaweeds concentrate iodine from the surrounding seawater. One report from British Columbia noted the iodine content in some species of *Laminaria* was 75,000 times higher than seawater (Druehl 2003). The function of iodine in brown seaweed is not clearly understood, although iodine supplementation to seaweeds grown in reef tanks has been associated with increased growth (Holmes 2003). Many studies have reported antibiotic effects of seaweed extracts (Biard and others 1980; Freile-Pelegrin and Morales 2004; González del Val and others 2001; Lustigman and others 1992; Pesando 1990; Pesando and Caram 1984; Sreenivasa Rao and Parekh 1981; Vlachos and

others 1997; Vlachos and others 1999); iodine may contribute to these effects either directly.

Health and iodine/seaweed intake

Iodine is an essential micronutrient in the human diet (De Benoist and others 2004). Adults require at least 150 µg/d, and inadequate iodine is associated with impaired mental function, mental retardation, and goiter. Iodine is especially important for normal fetal development. Iodine is rarely a problem for people living near a seacoast, but is common for people living inland. In addition, iodine deficiency is almost unheard of for people in Japan and Korea, where seaweeds are part of the normal diet. Based on widespread cultural acceptance of seaweeds as food, and mistrust of iodized salt programs, Chinese phycologists provided seaweeds to millions of inland-dwelling Chinese where they were readily incorporated into the daily diets. More than 90% of the Chinese population are now iodine sufficient (ChinaView. 2004).

Background

Archaeological evidence for the use of seaweeds is hampered by its easily degradable nature but it is likely that they have been part of traditional diets of coastal dwelling cultures worldwide. The oldest known use of seaweed dates to 13,000 years ago at a late Pleistocene settlement in Chile where archaeologists found seaweed remains near a shaman's hut at Monte Verde (Ugent and Tindall 1997). Other archeological evidence from ancient sites of the Jomon period in Japan (13,000 to 300 B.C.) (Arasaki and Arasaki 1983), indicate seaweeds have probably been included in folk medicine for many thousands of years. Three of the major medical traditions also have references to seaweeds: Ayurvedic (traditional medical tradition of India) from the 4th century BC

(Misra and Sinha 1979); Traditional Chinese Medicine, with its first reference to seaweed's medicinal qualities reportedly made by Shen-nung, in the Chinese "Materia Medica" of 2700 BC (Hoppe 1979); and in the "Ebers Papyrus," the Egyptian treatise on medical care, written approximately in 1550 BC (Loeser 1956). The medicinal uses of seaweed are vast and range from topical burn therapy to goiter therapy to softening of tumors (Schwimmer and Schwimmer 1955).

As food, seaweeds have been treasured by the nobility of Japan and China, as well as commoners such as fishermen living along the coast. Written reference to the high esteem people held for seaweed comes from Sze Teu (600 B.C.) who wrote, "Some algae are a delicacy fit for the most honored guests, even for the King himself"(Arasaki and Arasaki 1983). Japanese records from the 8th century indicate that over 30 kinds of seaweed were listed as acceptable forms of tax payments (Arasaki and Arasaki 1983). As an indication of the continuing high regard for seaweed in Japan, February 6th is celebrated as National Seaweed Day (Watts 2001). In a recent article on improving nutrition in Japan, public health officials recommended increasing seaweed consumption (Ikeda and others 2001).

Courtois first identified iodine in seaweeds(Rosenfeld 2000), and for over a century burning seaweeds were the primary source of iodine for medicinal purposes in conventional western medicine. It was not until the 1930s that a less expensive technique was developed to extract iodine from silver and saltpeter mining deposits(Chapman 1970). In the US, seaweeds continue to be used for soil enrichment, animal food supplements, stabilizers in dairy products, fat emulsifiers, various medical and industrial

applications, and more recently, as food and a natural source of iodine and other minerals in human health supplements.

The use of seaweed as a food is well established throughout Asia and the Pacific region. In Japan, 21 species of seaweed are routinely included in the diet, and in Korea more than 40 kinds of seaweed are commonly used as food (Arasaki and Arasaki 1983). Elsewhere in the Pacific basin, in Hawaii and other Polynesian islands, 29 kinds of seaweed have been reported as used for food, medicine, or as part of religious celebrations in pre-colonial times (Abbott 1978; Schonfeld-Leber 1979).

The average seaweed intake in Japan is approximately 4-7 g/d (Arasaki and Arasaki 1983; Matsuzaki and Iwamura 1981; Toyokawa 1978), with some estimates as high as 10 g/person/d (Fisheries Information Newsletter 95 2000). It is difficult to quantify the actual amount of seaweed consumed as it is often added as flavoring to noodles, soups, garnishes, and may be served as a snack, salad or side dish. Based on dietary intake surveys, the average daily iodine intake in these regions is between 500-1,000 µg/d (range from 200 to 20,000 µg/d), with most of the dietary iodine coming from seaweed consumption (Katsura and Nakamichi 1960).

Seaweeds are increasingly becoming common foods and food supplements in the US. As international foods have become commonplace throughout the world, seaweed consumption has increased. One study of marketing trends reported that 15% of Americans enjoy Japanese cooking (Sloan 2003). Advertisements for seaweed supplements claim that they provide an all-natural source of minerals, placing seaweeds in the dual roles of both normal food and nutraceuticals.

The bioavailability of the seaweed iodine to humans has been reported (Aquaron and others 2002; Marchal and others 2000; Meguro and others 1967) with the average seaweed intake in Japan between 7 and 10 g/d dry weight (Teas and others 2004), providing a similar amount of seaweed to people in clinical trials in the US posed a possible problem of excess iodine. Commonly consumed seaweeds have a wide range of iodine concentrations, and iodine excess could be an issue (Paul and others 1988) for people unaccustomed to eating seaweed.

How much iodine is present in a seaweed dish?

Food preparation and cooking methods are factors that must be considered when determining final the iodine content of foods. Iodine in seaweed is highly water-soluble. One study of the effects of cooking on kelp reported 99% of the seaweed iodine could be found in the cooking water after 15 minutes of boiling, (Ishizuki and others 1989). Although not specifically related to seaweed iodine, the cooking loss of iodine from iodized salt has been studied. Goindi (Goindi and others 1995) reported that the method of cooking was important in iodine loss, with losses ranging from 6% when roasted, to 20% when steamed or deep fried, to 27% when shallow fried, to 37% -82% with boiling (Expert Group on Vitamins and Minerals Secretariat 2003). Although these values are for iodine in other foods, it is likely that cooked seaweed would be subject to similar rates of loss.

In studies of iodine loss due to storage conditions, Marchal reported that iodine content remained more or less constant when stored in watertight bags or boxes. However iodized salt lost almost half of its iodine content in the first 40 days when stored in open containers or in paper bags, especially under humid conditions (Marchal and

others 2000), in which moisture might condense to concentrate water soluble iodine from the seaweed.

For many reasons, it is not simple to estimate the iodine content of dietary seaweed. For example, the iodine content of nori, the flat sheets of seaweed used to make sushi, contain trivial amounts of iodine (16 $\mu\text{g/g}$), but a bowl of miso soup made with a kelp-flavored stock, even without the presence of seaweed in the final soup, could contain more than 1000 μg of iodine. These sources of natural variation in iodine content contribute to the confusion in describing a particular species as “safe” for iodine sensitive individuals.

Although exposure to high concentrations of iodine will transiently decrease thyroid hormone synthesis for about 24 hours (acute Wolff-Chaikoff effect) (Wolff and Chaikoff 1948), continued exposure to excess iodine allows normal thyroid hormone synthesis to resume (Eng and others 1999; Wolff and Chaikoff 1948). However, some individuals do not escape or adapt to the transient decrease in iodine-induced thyroid hormone synthesis, i.e. those with autoimmune thyroid disease (Hashimoto’s thyroiditis), and continued excess iodine ingestion may induce hypothyroiditis (Braverman and others 1971). Thus, excess ingestion of seaweeds could, in susceptible subjects, induce hypothyroidism and, far less commonly in the United States, hyperthyroidism. Episodic dietary exposure to high iodine-containing foods could pose health risks for iodine sensitive patrons.

Preparation for Clinical Trials in Humans

Since the iodine in seaweed supplements would not be modified by either storage conditions or preparation, all the iodine would reach the stomach and therefore be

biologically available. It was therefore important for us to survey the iodine content of common dietary seaweeds before commencing a clinical study. Excess iodine intake can adversely affect thyroid function. The Lowest-Observed-Adverse-Effect Level (LOAEL), based on increases in serum TSH in thyroid function challenge tests, is 1,700 µg/d (US and Canadian RDI Committee)(Thomson 2002).

As a first step, we collected seaweed samples from health food stores in central Massachusetts, by contacting seaweed harvesters in Tasmania, Maine, and British Columbia, and collecting samples of kelp (*Laminaria* and *Ecklonia*) of known age and condition from Namibia(Teas and others 2004). All samples were in forms that an average consumer might buy, and included granules, capsules, as well as pieces of dried seaweed. Using conventional methods for analyzing iodine in foods and bodily fluids, we were able to rank seaweeds by their relative iodine content. The highest iodine-containing sample came from kelp granules made from Icelandic *Laminaria digitata*. The kelp granules were made of dried and pulverized seaweed. Figure 1 shows the relative iodine concentrations in common dietary seaweeds.

It is interesting to note that American wakame (*Alaria*) and kelp (*Laminaria*), although remarkably similar in appearance, had significant differences in iodine content, even when both specimens were harvested on the same day by the same harvester from the same bay.

Iodine has been reported to vary with age and condition of the plant, with iodine loss thought to occur rapidly once seaweeds are no longer growing. In a substudy of *Laminaria pallida* and *Ecklonia maxima*, both harvested in Namibia and of known age and growing conditions, we further investigated seaweed iodine concentration. Sun-

bleached seaweed collected from the beach had the lowest iodine content, followed by samples collected from floating drifts of seaweed (Figure 2). Samples cut from growing juvenile (< 50 cm) *Laminaria*, contained approximately twice the amount of iodine/g as found in samples from adult *Laminaria*.

In Figure 3 we further investigate the iodine content in different parts of a single seaweed sample. The iodine content measured in the inedible stipe was approximately half as high as that in the blade of *Ecklonia*, and was 20% lower in the *Laminaria* samples. Meristematic tissue, the growing area at the base of the blade of the seaweed, was also available for the Namibian *Laminaria*. The higher concentration of iodine in this area of the seaweed supports the idea that iodine is important to rapidly dividing seaweed cells.

Gall and his colleagues reported on the variation in iodine content in *Laminaria digitata* over a year and in different parts of the individual seaweed (Gall and others 2004). They found that iodine content was lowest during the summer, and similar to our study, was highest in younger *L. digitata*. These authors postulate that iodine concentration from seawater is dependent on the condition of the seaweeds, with more iodine depletion due to oxidation associated with the mechanical stresses of wave action on older parts of the blades and the photo damage of bright sunlight during warmer summer months. In addition, endo- and epiphytic stresses which are greater in the summer could further stimulate iodine efflux as responses to biotic stresses.

The variation in iodine content was profound, reflecting harvesting condition differences such as season, age and condition of the seaweed, temperature of the water, and geographic location. In Table 2 seaweed iodine contents of different seaweeds are

compared. For example, iodine in wakame (*Undaria*) was 23 times higher in the sample from China, and 2.5 times higher in the samples analyzed by Lee (Lee and others 1994) than in the samples we analyzed from New Zealand, Australia, and Japan. Kelp varied from an average of 1440 µg/g in the kelp (*Laminaria*) the nutritional analysis presented by Maine Coast Sea Vegetables(MCSV 2005) to 5307µg/g in the values reported for French *Laminaria* (Aquaron and others 2002). The lower amounts of iodine in the MCSV could be due to the diverse sources of seaweed provided by the freelance harvesters who might collect drift kelp as well as cut growing *Laminaria*. The red seaweeds (*Rhodophyta*) in our analysis and those of others were consistently lower in iodine, less than 100 µg/g.

Clinical Studies of Seaweed Supplements

In our clinical study postmenopausal women, we sought to answer two questions. First was whether the iodine in seaweed would be bioactive in a similar way to iodine in other foods, and second whether women who had been treated for early breast cancer might have a different way of metabolizing iodine. We therefore recruited 15 women who had never been diagnosed with breast cancer and 10 women who had been treated for early (Stage I, or II) breast cancer but were disease free at the time of the study. All 25 women were healthy, with normal thyroid function (thyroid stimulating hormone levels either < 0.4 or > 4.5 µU/ml TSH).

Alaria esculenta, also known as American wakame, a low-iodine (95 µg/g) containing seaweed was used as a seaweed supplement. To mimic the exposure of Japanese women to seaweed, women were randomized to either six weeks of 5-g/d

seaweed powder (10 capsules) each evening with the last meal of the day, or six weeks of 5-g/d maltodextrose in 10 identical gelatin capsules.

Having ever been diagnosed with breast cancer was not associated with any significant differences in responses to seaweed supplements. When seaweed supplementation periods were compared to placebo periods, the only effects were significant increases in urinary iodine excretion after six weeks of seaweed intake and a small but statistically significant increase in serum (TSH). On average 266 $\mu\text{g I/d}$ were excreted while taking placebo supplements, and 587 $\mu\text{g I/d}$ while taking seaweed.

In addition to the traditional use of seaweed for goiters and the empirical success of the Chinese seaweed supplementation program for iodine deficiency, this clinical study supports the idea that seaweed contains biologically available iodine, and that consuming seaweed supplements would affect thyroid function. The changes in TSH were small and although statistically significant, the values remained well within normal ranges and were unlikely to be physiologically important. However, some common dietary seaweeds, especially some of the kelps (*Laminaria*), can contain 40 times as much iodine as did the supplements in our study. The small changes we observed in euthyroid women may not be representative of the effects of high iodine kelp in the general population.

Two other clinical studies have reported on the bioavailability of iodine from seaweed. Clark et. al. conducted a similar double-blind prospective six-week clinical trial in 36 healthy euthyroid subjects (Clark and others 2003). The study compared high dose kelp (1,000 $\mu\text{g iodine/d}$) and low dose kelp (500 $\mu\text{g iodine/d}$). The high dose seaweed supplement provided twice as much iodine as was given in our study, whereas

the low dose was approximately equal to what we provided.. TSH increased significantly in both kelp-supplemented groups and T3 decreased significantly after high dose kelp therapy.

A second study of iodine bioavailability from seaweed focused on the question of host iodine status. Aquaron et. al. reported on the 48-hour short term effect of dietary seaweed (*Laminaria*) in two different geographic locations. In healthy iodine-replete volunteers in Marseille, France, 90% of the seaweed iodine was excreted, but in a mildly iodine deficient population in Brussels, Belgium, only 62% of the seaweed iodine was excreted within 48 hours (Aquaron and others 2002).

Another factor reported to affect iodine metabolism is the activity level of the person eating the seaweed and the climatic conditions at the location of the study.. In a group of Japanese male university students, iodine losses in sweat during athletic training were high, suggesting that exercise or even just living in hot, humid climates could increase iodine daily requirements (Suzuki and Tamura 1985). These factors were not described in the clinical studies done to date and including exercise and ambient weather conditions in future studies will be important.

In Japan and Korea, exposure to high iodine containing foods usually begins *in utero* and via breast milk (Moon and Kim 1999). Seaweed soup is recommended to women after giving birth, resulting in high iodine containing breast milk (Moon and Kim 1999). Any effects of the high iodine exposure to the newborn infants have always been assumed to be trivial and transient. However, this may not be true. In Moon's study (Moon and Kim 1999) of 50 lactating Korean mothers, the average maternal iodine intake immediately postpartum was 2744 µg/d, or almost three times the daily intake

recommended by the World Health Organization, decreasing to 1295 $\mu\text{g}/\text{d}$ at 4 weeks. Exposure of the infants to iodine was very high during the first few days postpartum, with iodine concentration in colostrum being 2170 $\mu\text{g}/\text{l}$. By four weeks postpartum, this level had decreased to 892 $\mu\text{g}/\text{l}$ in breast milk. This extraordinary exposure to iodine during the perinatal period may not be without risk to the infants. Nishiyama and colleagues reported on urinary iodine excretion of 34 infants in a study in Kumamoto Japan, 15 of whom were diagnosed with thyroid dysfunction due to their mothers' intake of seaweed during pregnancy (Nishiyama and others 2004). They estimated that half of the women ingested between 2300 to 3200 μg iodine/d, and the others ingested from 820 to 1400 μg iodine/d. Although such high iodine exposures are likely to be normal, twelve of the fifteen infants were given medication to regulate thyroid function. This study supports the idea that in Japan and Korea, infants are normally exposed to high levels of iodine, and these perinatal exposures may be important in understanding how adults living in these countries might be habituated to high daily levels of dietary iodine.

Given the high exposure to iodine in infancy and adulthood, adult thyroid dysfunction might be expected. Very high intakes of seaweed (more than 25 g dried wt/d) have been associated with both hypo and hyperthyroidism (Konno and others 1994). Theoretically, the chronic high-iodine seaweed consumption by people in Japan and Korea could contribute to health problems associated with excess iodine. However, thyroid disease is less common in Japan than in the US. The prevalence of hyperthyroidism ($\text{TSH} < 0.15 \mu\text{U}/\text{L}$) among 4110 people living in the capitol of Sapporo on Hokkaido in Japan was 0.6%, increasing to 1.1% among people living along the Hokkaido seacoast (Konno and others 1994). By comparison, the prevalence of

hyperthyroidism ($TSH < 0.1 \mu U/L$) among 13,344 adults with no underlying thyroid problems in the US was 1.3 % (Hollowell and others 2002). Figure 4 presents these comparisons. Hypothyroidism ($TSH > 5.0 \mu U/L$) prevalence in Japan was also lower, with a rate of 1.3% in Sapporo and 3.8% along the coast (Konno and others 1994). The US prevalence of hypothyroidism ($TSH > 4.5 \mu U/L$) was 4.6% (Hollowell and others 2002). Figure 5 presents these comparisons.

Cancer and Seaweed

A) Thyroid Cancer

Since seaweed iodine might place a strain on thyroid function, thyroid cancer could be a possible concern for people eating high iodine diets. However, when age standardized incidence of thyroid cancer rates were compared, thyroid cancer rates were higher in the US (6.2/100,000), compared to Japan (4.8/100,000). Unexpectedly, for those people in Japan who develop thyroid cancer, death rates are twice as high in Japan (0.6/100,000) as in the US (0.3/100,000) (Ferlay and others 2001). Japanese immigrants to the US have higher rates of many cancers, including thyroid cancer (Tominaga 1985). Using autopsy studies to estimate the rate of undetected thyroid cancer at death, the prevalence in Japan was 35% (Miller and others 1993), compared to 3.6% in the general US population (Wang and Crapo 1997). This ten-fold difference suggests that factors such as diet or environment may play a role in thyroid cancer initiation but possibly in Japan dietary iodine may also protect against cancer progression. Figure 6 presents these comparisons.

B) Digestive Tract Cancers

Since seaweed is a food and comes directly into contact with the gastrointestinal mucosal lining, and since stomach cancer rates are high in Japan, it is also important to consider the possibility that seaweed might contribute to these higher rates. Seaweed intake is rarely included in cancer and dietary assessment, but there have been five epidemiologic studies done in Japan that have included frequency estimates of seaweed intake. Four of the studies have found significant reductions in cancer risk associated with increasing seaweed consumption. Eating seaweed two or more times/week showed a highly significant reduction in risk ($p < 0.0001$) (Hoshiyama and Takafumi 1992) of both single and multiple stomach cancers, a significant reduction in esophageal cancer (Nakachi and others 1988), a significant reduction in rectal cancer ($p = 0.01$) and in two studies of colon cancer, one study reported a significant reduction in risk ($p < 0.01$) (Hoshiyama and others 1993) whereas the second study reported a non-significant reduction in colon cancer ($p = 0.59$) (Hoshiyama and others 2000). A difference in definition of seaweed intake frequency distinguished the two studies, with ingestion 5 or more times a week being highly protective, but two or more times being only weakly protective. These two studies give some estimate of a dose response relationship between seaweed and cancer protection. These studies are compared in Figure 7.

C) Breast Cancer

Although little is known about relative breast cancer risk and seaweed intake among humans, a small body of research, both *in vivo* and *in vitro*, suggests seaweed may be useful in breast cancer prevention. Seaweeds are specifically used to treat tumors in Traditional Chinese Medicine and Japanese folk medicine. On a population level, those people for whom seaweed is a regular part of their diet, most notably in Japan, have

dramatically lower rates of hormone sensitive cancers, both of the breast and prostate (Hebert and others 1998; Hebert and Rosen 1996; Kodama and others 1991).

Epidemiologic studies done in Japan in the 1980s, before Westernized diets were common, found that Japanese women had 1/3 the rate of premenopausal breast cancer and 1/9 the rate of postmenopausal breast cancer (Reddy and others 1980). In addition, when a Japanese woman developed breast cancer, she was more likely to survive at least five years longer than a woman diagnosed with breast cancer in the United States (Morrison and others 1973).

No clinical studies of breast cancer and seaweed have yet been done, in a large prospective dietary study 21,852 Japanese nurses in Japan, investigators reported after 9 years of follow-up, that high intake of miso (fermented soybean paste) soup was the food most closely associated with the lowest breast cancer risk (Yamamoto and others 2003). This is particularly interesting since an in vivo study compared dietary water extract to powdered food to injected extract, and reported that dietary water extract was the most effective against induced tumors (Yamamoto and others 1986). Since miso soup is a hot water extract of seaweed with a tablespoon or less of miso and usually a few vegetables added it is very suggestive that seaweed and seaweed soup consumption may help explain the lower breast cancer rates of women in Japan. Women who had miso soup three or more times per day had about half the rate of breast cancer (RR0.51; 95% Confidence Interval 0.32 to 0.83). Two other epidemiologic studies of diet and breast cancer in Japan also reported lower rates of breast cancer were associated with increased miso soup consumption, with 15% reduction for women who had consumed it daily vs. non-daily (Hirayama 1990) and 13% reduction for women who drank miso soup more

than five times versus less than one time/week(Key and others 1999). The three studies are presented in Figure 8.

Iodine deficiency may be a risk factor for breast cancer (Smyth 2003a; Smyth 2003b; Venturi 2001). Additionally, some physicians have reported therapeutic success using oral elemental iodine solution for breast fibrocystic disease (Ghent and others 1993; MacFarlane 1993). Iodine is critical for the health of newborn infants, and during lactation iodine is concentrated in breast milk and is found in rapidly dividing breast cells. When rapidly dividing breast cancer cells are present in the breast, iodine may also play a role, although the exact mechanism is unclear. Breast cancer cells have lower iodine content than nearby healthy breast cells(Venturi 2001), and the work of Funahashi and colleagues report protection from dimethylbenzanthracene (DMBA)-induced mammary tumors when iodine was given to the rats in their diet. As a possible mechanism, they reported a high correlation between serum iodine and apoptosis of mammary cancer cells (Funahashi and others 2001; Funahashi and others 1996; Funahashi and others 1999). These results, along with those of Teas and others (1984) and others (Maruyama and others 2003; Takahashi and others 2000; Yamamoto and others 1987) have reported for dietary seaweed as inhibitory of DMBA-induced mammary tumors are consistent with the idea that seaweed, possibly via iodine, could be involved in breast cancer prevention.

HIV and algae

Seaweeds are regularly consumed in Japan and Korea, where for more than 20 years, rates of HIV infection have remained at less than 0.1% of the adult population(UNAIDS 2002). *In vitro* studies using a water extract of *Undaria* added to

HIV infected cells resulted in the disappearance of almost all HIV infected cells, strongly inhibiting HIV viral adsorption and fusion (Muto and others 1992), as well as inhibited HIV reverse transcriptase activity. Synergism between AZT, one of the common antiretroviral drugs and seaweed increased AZT – induced reverse transcriptase inhibition by an additional factor of 10 (Sugawara and others 1989). Furusawa reported that *Undaria* extract in an *in vivo* AIDS model using erythroleukemia was as effective as AZT(Furusawa and others 1991).

The most likely mechanism of action is as an inhibitor of HIV fusion to lymphocytes, thereby preventing on-going transmission of infection in the blood. Other studies of seaweed extracts have demonstrated antiviral effects against a range of enveloped viruses, including retroviruses (SIV and HIV)(Luscher-Mattli 2000; Schaeffer and Krylov 2000; Witvrouw and De Clercq 1997)and HIV-associated DNA herpes viruses (HSV-1 and HSV-2, CMV, and EBV)(Cooper and others 2002; Santos and others 1999). Anecdotal reports suggest that seaweed inhibits HIV and increases CD4 lymphocyte counts in people with HIV(Teas and others 2005). To explore if dietary algae could explain some of the anomalies of worldwide HIV/AIDS incidence, we have an ongoing clinical study to determine whether oral algae could affect HIV viral load or immune parameters associated with HIV/AIDS (CD4 helper cells, CD8 suppressor cells, and CD3 total T lymphocytes). The results, although preliminary, are encouraging and appear to be consistent with *in vitro* and *in vivo* studies of HIV and algal extracts. If these results are maintained in larger studies of HIV-infected individuals followed for longer periods of time, seaweeds as food or as a food supplement in the form of tablets or capsules could provide an inexpensive, non-toxic therapy that could be used immediately

by some of the 40 million people who currently live with HIV/AIDS. The extensive testing required of drugs and the costs associated with patenting would not apply to whole seaweeds, as they are naturally occurring widely available food. This is especially important, since more than 90% of the people who meet the criteria for antiretroviral treatment either can not afford such treatment or it is unavailable. The possibility that a dietary alga or combination of algae could affect the progression of HIV/AIDS deserves more attention and research.

Future Directions

Seaweeds appear to be food as well as active nutraceuticals in the Asian diet. The iodine content may be an important factor in maintaining healthy thyroid function, although it is also possible that only iodine-tolerant individuals have survived the high seaweed iodine content of maternal diets during the perinatal period. Epidemiologic data strongly suggests that eating seaweed at least once a day for Asian populations could be associated with significantly lower risks of various cancers. The role of iodine in cancer has been largely unexplored, although several researchers have proposed that iodine is critical to breast health. Animal studies and *in vitro* work support these hypotheses. The *in vitro* studies of seaweed extracts also support a protective role for seaweeds in protecting against viral diseases and enhancing immune function. Epidemiologic data and preliminary clinical data are congruent for a protective role of seaweeds in preventing or mitigating the effects of viral infections such as HIV. Due to cultural biases of non-Asian countries, seaweeds have long been ignored as significant dietary factors. As clinical and laboratory research identifies seaweed-specific metabolic

pathways, further investigations of these little appreciated dietary condiments may prove their worth in maintaining health.

Seaweeds, both in the US and even in Japan and China, are becoming more frequent topics of research, although most attention has focused on seaweeds as sources for pharmaceutical drugs. More research on whole foods is needed.

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